SUMMARY MINUTES

SIXTY-EIGHTH MEETING OF THE OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL

OPEN SESSION

June 3, 2004

Holiday Inn Gaithersburg
Gaithersburg, Maryland

Obstetrics and Gynecology Devices Advisory Panel Meeting

Open Session June 3, 2003

Attendees

Chairperson
Kenneth L. Noller, M.D.
Department of Obstetrics & Gynecology
Tufts University Medical School

Executive Secretary
Joyce M. Whang, Ph.D.
OBGYN Devices Group

Assistant Executive Secretary
Mike Bailey, Ph.D.
OBGYN Devices Group

Voting Members
Susan M. Ascher, M.D.
Department of Radiology
Georgetown University Hospital

Andrew I. Brill, M.D.
Department of Obstetrics and Gynecology
University of Illinois at Chicago

Carol L. Brown, M.D.
Weill-Cornell Medical College
Memorial Sloan-Kettering Cancer Center

Lawrence A. Crum, Ph.D.
Center for Industrial and Medical Ultrasound
University of Washington

Ralph B. D'Agostino, Ph.D.
Mathematical Statistics Department
Boston University

Michael P. Diamond, M.D.
Department of Obstetrics and Gynecology
Hutzel Hospital / Wayne State University School of Medicine

Evelyn R. Hayes, Ph.D.
College of Health and Nursing Sciences
University of Delaware

Paula J.A. Hillard, M.D.
Department of Obstetrics & Gynecology and Department of Pediatrics
University of Cincinnati College of Medicine

Grace M. Janik, M.D.
Department of Obstetrics & Gynecology
Medical College of Wisconsin

Hugh Miller, M.D.
Department of Obstetrics and Gynecology
Arizona Health Science Center

Kenneth E. Najarian, M.D.
Department of Radiology
University of Vermont College of Medicine

Anne C. Roberts, M.D.
Department of Radiology
UCSD Medical Center/Thornton Hospital

Thaddeus V. Samulski, Ph.D.
Department of Radiation Oncology
Duke University Medical Center

Stephen B. Solomon, M.D
Department of
Cardiovascular/Interventional Radiology
Johns Hopkins Hospital

Jonathan W. Weeks, M.D.
Suburban Hospital, Maternal-Fetal
Medical Center
Louisville, KY

Bradford J. Wood, M.D.
Diagnostic Radiology Department,
National Institutes of Health

Consumer Representative
Kleia R. Luckner, J.D., M.S.N.
Women's Ambulatory Health
The Toledo Hospital

Industry Representative
Mary Lou Mooney, R.A.C.
SenoRx, Inc.

FDA Representatives
Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices

Julia A. Corrado, M.D.
Office of Device Evaluation

Kathryn S. Daws-Kopp
Office of Device Evaluation

Bruce A. Herman
Office of Science and Engineering
Laboratories

Noel del Mundo, M.D.
Office of Device Evaluation

Colin Pollard
Chief, Obstetrics and Gynecology
Devices Branch

Loren Zaremba, Ph.D.
Office of Device Evaluation

CALL TO ORDER

Panel Chair Kenneth L. Noller, M.D., called the meeting to order at 8:30 a.m. and asked the panel members to introduce themselves. **Panel Executive Secretary Joyce M. Whang, Ph.D.,** stated that there would be no OB/GYN Devices Panel on July 26 and 27, 2004; the remaining panel meeting dates for this year are October 25 and 26, 2004. She introduced one new voting member, Paula J. A. Hillard, M.D. Dr. Whang read into the record the appointment of eight temporary voting members: Susan M. Ascher, M.D., Andrew I. Brill, M.D., Lawrence A. Crum, Ph.D., Ralph B. D'Agostino, Ph.D., Grace M. Janik, M.D., Anne C. Roberts, M.D., Thaddeus V. Samulski, Ph.D., and Bradford J. Wood, M.D. She then read the conflict of interest statement. Full waivers were granted to Drs. Asher and Roberts, allowing them to participate fully in the meeting; limited waivers granted were for Michael P. Diamond, M.D. and Stephen B. Solomon, M.D. for their interests in firms that could potentially be affected by the panel's recommendations, allowing them to participate fully in the panel discussions but excluding them from voting. The Agency took into consideration other matters regarding Drs. Diamond and Solomon, who reported current interests in firms at issue but in matters not related to the day's agenda; they could participate fully in the panel's deliberations.

Colin Pollard, Chief, Obstetrics and Gynecology Devices Branch, welcomed the panel and noted that they would be looking at a pre-market approval application (PMA P040003) from InSightec, Ltd. for the ExAblate®, a high intensity focused ultrasound system for the treatment of uterine fibroids in pre- and perimenopausal women. This is a new surgical modality that uses conventional MR imaging for pre-operative treatment planning and MR thermal mapping. Treatment of uterine fibroids is

the first indication coming before the Center in a PMA. He noted that FDA put together a "designer" review team from all parts of the Center, especially from the technical side. The review was expedited based on unique features and advantages of the product. The FDA review is still ongoing but Mr. Pollard said that they felt it was appropriate to hear panel input on the product as the Center works through the various review issues.

OPEN PUBLIC HEARING

No comments were made.

INSIGHTEC, LTD. PRESENTATION: P040003

Rob Newman, MS, RAC, began the sponsor's presentation by introducing his colleagues from InSightec. Mr. Newman noted that the device is indicated for use in pre- and perimenopausal women with symptomatic uterine fibroids that are visible on noncontrast MRI and enhance on contrast MR. The only applications allowed in the United States and Canada are for investigational use. The system is commercially available in Europe, Israel and Japan, and about 600 women have been treated worldwide.

Elizabeth Stewart, M.D., associate professor of gynecology, clinical director, Center for Uterine Fibroids, Harvard Medical School and Brigham and Women's Hospital, introduced the device, noting that uterine fibroids are a serious clinical problem for women. She covered the costs, both economic and personal, of the condition. Estimates for prevalence rates ranges from 20% to a more recent estimate of 75% in high-risk populations for clinically detectable fibroids. Uterine fibroids limit work

interaction for many women and impair their general quality of life, often with extreme pelvic and bladder discomfort. Better therapies for uterine fibroids are called for, she added.

Dr. Stewart covered the treatment options, but noted these treatments are generally restricted to women with structurally normal uteri. She presented the pros and cons for hysterectomies, myomectomies, uterine artery embolization (UAE), thermal ablation, and drug therapies.

Many women do not want to take time for the more invasive procedures or fear the procedures. For these women, Dr. Stewart said MRI guided focused ultrasound surgery (MRgFUS) will be a very important option. It is a noninvasive outpatient procedure, spares the uterus, and targets only specific fibroids, avoiding the myometrium or the endometrium. Real-time feedback on temperature gives the clinician important information about thermal ablation.

Mr. Newman continued the presentation by reviewing some of the key points of the device. He noted that the device is a combination of two items: focused ultrasound as a source of thermal energy, and MR to plan and control the treatment in progress. The device is made up of two main components. The first is the patient table and electronics attached to the MR system, with a transducer and a water bath. Energy is transmitted through the abdominal wall and focuses on a point in the body. The other component is the operator control consol. He also covered the evolution of MR guided focused ultrasound, as well as how the transducer concentrates the energy. Mr. Newman noted that energy density in the far field area is reduced by beam divergence and absorption. He added that this device is unique because the procedure ablates one small area at a time

with individual sonications, versus a cryoprobe than can create a large lesion. The system ablates one 0.5 cm^3 at a time and a single sonication takes about 20 seconds to raise temperature 65-85º C degrees centigrade. Normal body temperature is maintained just a few centimeters from the sonication site.

MR thermometry checks tissue temperature and is accurate within 3º C, with images displayed at 3-second intervals during energy delivery. Mr. Newman noted that the system measures change in temperature relative to body core temperature, not absolute temperature of the tissue. He added that they have done extensive thermal modeling of tissue response, including work on focusing the transducer and cavitation avoidance.

Clare M. C. Tempany, M.D., professor of radiology, director of Clinical MRI, Harvard Medical School and Brigham and Women's Hospital, addressed the use of MRI to visualize fibroids to determine if they are eligible for treatment, and summarized the many types of fibroids.

She also walked the panel through a typical clinical treatment, including what the patient's activities the night before and morning of the procedure. Shaving, she noted is very important, because hair can interfere with the beam. Intravenous conscious sedation is used, as is a Foley catheter to control bladder movement. Dr. Tempany stressed that the nurse remains in the room with the patient and that the patient and the nurse always maintain the ability to terminate an individual sonication. A pain medication is typically given at the beginning of the procedure, with subsequent varying doses based on the pain reported by the patient.

Dr. Tempany reminded the panel of the interactive nature of the treatment; for example, the beam path is checked prior to each sonication, accommodating irregularities in the skin's surface and the beam's relationship to the bowel, and there is constant direct physician control of each sonication. She closed her presentation by noting the considerations taken for the patient's safety, including coaching the patient on the importance of remaining absolutely motionless during the procedure; using conscious sedation and a Foley catheter to help the patient remain still; using fiducials at the beginning and end of each sonication to note any patient motion; and adding that the operator receives real-time feedback on any patient motion.

Dr. Stewart next discussed the design of the clinical trial and its results. Women in the feasibility study were often reluctant to undergo the therapy and hysterectomy, so recruitment suffered. Three other sites began recruiting patients, and the Israeli National Health Service made hysterectomy optional for their group, believing it unethical to require women to undergo MRgFUS without the ability to opt out of definitive therapy. The study followed all of these patients, however, and reported them together. There was a single hospitalization for control of nausea, but very little pain was reported in most patients and many did not take OTC painkillers within 72 hours of treatment. The sponsor learned from experience in the feasibility study to pay special attention to shaving and catheter use. They used information from this study to embark on the pivotal study. Extensive negotiation with the FDA and the investigators resulted in selecting abdominal hysterectomy as the alternative treatment.

The pivotal study design was an open, non-randomized trial for women who would undergo the MRgFUS treatment, with 6-month follow-up. The study was later

modified to extend follow-up to 12-, 24-, and 36-month follow-up. The control group women received total abdominal hysterectomies (TAH) with 6-month follow-up. She noted that employing a sham or placebo treatment would have been difficult. The TAH arm had 71 patients, while the MRgFUS arm enrolled 106 patients.

Dr. Stewart covered the pivotal study's inclusion criteria, noting that patients' Uterine Symptom and Quality of Life Symptom Severity Sub-scale was required to exceed 40.6 (on a scale of 100). Exclusion criteria were any contraindications to the use of MR, uterine size greater than 24 weeks, patient weight greater than 250 pounds, and an undiagnosed pelvic pathology other than the fibroids. The primary hypothesis was that the MRgFUS would result in a 10-point SSS improvement at 6 months for at least 50% of the treated patients. Secondary hypothesis stated that the incidence of significant clinical complications would be lower and the recovery speed would be greater for the MRgFUS group versus the TAH group.

Among the MRgFUS group, 70.6% reported at least a 10-point improvement in their SSS. Efficacy results included significant improvement in patients' SSS at 6 months and a mean reduction in the SSS score of 23.8 points (a reduction of about 40 percent). Although the original approved protocol and consent included follow-up only at 6 months, the sponsors were able to contact 61 patients at 12 months; 83 percent of this group reported that they were satisfied with the treatment; however, in the intent-to-treat group at 12 months, 48% had a greater than 10 point improvement in the SSS score. The MRgFUS group experienced a 12% rate of significant clinical complications, while the hysterectomy group experienced a 46% rate. One common problem they noted was

fibroid return, but she suggested that this might be improved by optimization of the treatment.

Dr. Stewart said that there was only one significant adverse event related to the use of the device: a patient noticed a skin burn during treatment and weakness in the lower leg immediately after the treatment, with evidence of sacral nerve injury. However, this patient made good recovery by 12 months, and was running a marathon. There was one death unrelated to the procedure in a patient outside the United States with unidentified thrombotic risk features.

The continued access study in the United States began April 2003. Follow-up will continue through 36 months, and there have been some minor changes in treatment protocols. To date, 89 patients have undergone the procedure, and the adverse effects in this group are 30 percent lower than in the pivotal study.

Mr. Newman covered issues around training. He noted that the system will only be used under direct supervision of trained physicians with gynecology and radiology experience. The first treatments will be supervised and all treatments will be recorded for review so that everyone can learn from each procedure. Experience and training will then be ongoing. In fact, they have a log of every treatment ever done.

Dr. Stewart closed the sponsor's presentation by noting that the device has very low incidence of device-related adverse events, decreased risk of anesthesia-related events, and clinical improvement of patients' symptoms, while preserving the uterus and on an outpatient basis.

FDA PRESENTATION

Kathryn S. Daws-Kopp, lead reviewer, began the FDA's presentation. She described the history of the regulatory actions with the sponsor. The sponsor came to the FDA General Surgery Division in 2000; The Obstetrics and Gynecology Devices Branch took over review in late 2001. The pivotal study was given conditional approval in March 2002 and full approval in May 2002. The sponsor received conditional approval of a continued access study in June 2003 and full approval August 2003. The PMA was submitted January 2004 and received expedited review status.

Ms. Daws-Kopp described the components of the ExAblate® device, noting that the device is commercially available for 1.5T for MRI use, but is not commercially approved for thermography. She reviewed indications for device use, and covered what FDA looked for in their review, including electric shock, unintended burns, EMI shielding, adequate targeting, thermal dose delivery, compliance and design control, and manufacturing issues.

She noted a number of major ongoing issues, including thermal accuracy, adverse events and mitigation of these events, control group comparability, pre-approval inspection of the manufacturing facility, and labeling—but she said that FDA would not cover the last two items during the presentation as they are not completed.

Julia Corrado, M.D., OBGYN Devices Branch, discussed two of the feasibility study centers (in the United States and Britain), the pivotal study, and the continued access study. She summarized the pathology results from the Brigham and Women's Hospital study site, stressing two findings: that the volume of the necrosis was sometimes

larger than the treated areas, and that in one case microscopic coagulation necrosis extended 1-2 mm beyond the fibroid capsule. Dr. Corrado noted the adverse event of sciatica in Israel that, in hindsight, they might not have fully appreciated at the time. Symptoms began improving for this patient at about 2 to 3 weeks after the treatment.

She also noted that FDA has worked with the sponsor on the pivotal study design, focusing on adverse effects, especially necrosis of the tissue beyond the uterus. This prompted a very conservative treatment planning program. The agency felt it would be prudent to limit the volume of tissue to be targeted, given that the volume effect has been greater than the targeted volume and that the treatment is so new.

In addressing the pivotal study, Dr. Corrado discussed the demographic differences in the two arms of the study. There was little difference in age between the two study arms, although average BMI was higher in the hysterectomy group. This group also had higher percentage of African Americans (34%) and higher prevalence of diabetes and other chronic conditions.

Dr Corrado noted that there are two ways to look at study success: intent to treat, in other words, all patients enrolled; and evaluable analysis, a way to look at the analysis that does not count subjects as failures who were not actual failures. The study's 70.6% effectiveness rate at 6 months among the intent to treat group (109) was well above the required 50% for success. However, the hysterectomy patients at 6-months follow-up were more likely to say they were satisfied than the ExAblate® group after 6 months.

She also looked at the intent-to-treat group at 12 months, which showed an effectiveness rate of 38.5%, a considerable drop from 6 months. However, she noted that the sponsor was informed late in the pivotal study that they would be required to follow-

up for 36 months. Patient retention became an issue. This may help explain the drop in the success rate at 12 months, she said; if they declined to participate or could not be found, they were considered failures.

Dr. Corrado next addressed the safety-related issues, specifically skin burns and nerve injury. The FDA believes that these two injuries are unique to the ExAblate® procedure. She then discussed the continued access study, which FDA approved to include more liberal treatment activities.

Loren A. Zaremba, Ph.D., Radiological Devices Branch, discussed the advantages and disadvantages of MR thermal mapping in the ExAblate® for the treatment of uterine fibroids. He highlighted the safety and reliability concerns the FDA has about MR thermal mapping, specifically their concerns about 1) whether temperature measurements can be made in all areas of interest; 2) whether these measurements are sufficiently accurate; 3) whether the measurements can be made in a timely manner to allow for adjustments; 4) the frequency of failure; and 5) whether the back up is adequate. He added that MR thermal mapping provides significant advantages over other technologies for guidance of focused ultrasound treatment. Its major limitation is that it cannot measure temperature in the sacral nerves, bone, or fat, which prevents estimation of the heating of these and other items in the far field. The issues related to motion sensitivity and lower temporal and spatial resolution are not serious, and calibration can be improved with additional studies.

Bruce Herman, Office of Science and Engineering Laboratories, continued the FDA's presentation with a discussion of possible adverse thermal effects of the ExAblate® device. He advised that cell damage thresholds are not simply a matter of the

peak temperature of an energy beam, but of temperature combined with exposure time. Temperature of the structure is a factor of local intensity, absorption of ultrasound by the structures, the incidence of the ultrasound beam on the bone, beam and structure size, thermal characteristics of the tissues, and geometry—meaning how close one structure is to another.

Mr. Herman also looked at factors that could cause temperatures to rise higher in tissues and structures than in models. They include higher absorption rates, larger structures, structures closer to the bone or focus area, inaccuracy of the MR temperature map at the focus site, incorrect thermal conductivity or heat capacity, and possible overlap of consecutive sonications. He ended his discussion noting that models using generally accepted values for tissue parameters, with 40 mm bone standoff, predict that thermal adverse effects will be rare. However, because of the range of reported and possible tissue and structure variations, as well as MR inaccuracies, adverse thermal effects cannot be totally ruled out. Therefore, clinical results take on added importance when evaluating the modeling accuracy and the actual risk and benefits.

Noel del Mundo. M.D., OBGYN medical officer, presented the safety analysis of sonication-related adverse events that occurred during the pivotal trial. The most notable adverse events were skin burns and nerve injuries. In the pivotal trial, five cases of first or second degree burns emerged. This probably occurred, he said, because of improper acoustic coupling between the skin and the gel pad due to improperly shaved skin, a skin fold, oil on the skin, or air bubbles in the coupling and, in one case, patient movement. Dr. del Mundo suggested that additional training could reduce these events. In fact,

follow-up results on 54 patients in the continued access study have shown no cases of skin burns.

He next addressed the five cases of nerve injuries reported during the pivotal trial, with symptoms lasting from 2 days to 12 months. There were also three cases of "nerve stimulation" in which the patients experienced leg pain in the last few seconds of sonication; symptoms resolved the same as treatment. The worst case was Patient 9019. Assessment by a neurologist at 6 months indicated that injury consistent with neuropraxia had resolved, but that some minor symptoms would take longer to resolve. By 11 months, Patient 9019 had almost fully recovered and returned to her baseline activity level. It is believed that the patient sustained injury to the sacral nerve bundle.

Dr. del Mundo next covered the mitigations implemented by the continued access study, including adjusting the transducer angle to decrease bone energy absorption and setting a minimum distance between treatment focus and the sacral nerve and the sacrum. However, while there are no reported skin burns in the continued access study, due to modified operator training protocols, nerve injuries are still present in a few patients despite implementing the mitigations. He asked that the panel also address in their discussions whether additional mitigations are warranted.

OPEN PANEL DISCUSSION

Because there was some time remaining before lunch, Dr. Noller asked the panel members to present questions to the FDA or the sponsor for responses after lunch. Panel members asked why the SSS was considered an appropriate measure and whether there was too much variability inherent in this measure. Others asked why the sponsors settled

on a 10-point improvement in the SSS. Panel members also raised the issue of a placebo effect and the use of multiple parameters.

Dr. Stewart responded to the panel's questions. The study used the SSS because symptomatolgy is the major complaint for women with uterine fibroids. This was the only fibroid-specific validated measure, and the SSS score of the UFSQOL is the appropriate measure for this disease. The 10-point improvement was defined at the outset of the study for two very different reasons: an improvement of 10 points translated into a clinically significant improvement in symptoms; and due to several methodologic reasons, including the fact that 10 points was very close to the standard deviation in the population, very near to the standard error of the mean, and correlated with a moderate effect size.

As far as variations between the screenings, the treatment day assessment of symptom severity and the follow-up assessments are very consistent—only the screening day assessment showed any variability. Dr. Stewart suggested that this could have been because some centers were not administering it in the standard format; they were using phone or fax communication instead of face-to-face interviews to assess symptomatolgy. However, she reported that there were no meaningful differences in which measurement was used. As far as placebo effect, she acknowledged that while any self-reported measure is vulnerable to a placebo effect, the investigators have documentation of actual physical changes, including blood flow, radiographic imaging, and MRs, as well, at six months patients were still reporting diminished menstrual blood flow and bladder pressure. She added that, from UAE experience, they know that reduction in the size of the fibroid does not necessarily equate efficacy. Finally, she noted that the study did use

multiple parameters in addition to the SSS, including SF36 monitoring to prove concordance in the study sample.

PANEL QUESTIONS

Dr. Noller read the FDA's definitions of safety and efficacy that the panel should consider when making their decision about the device. In response to a question about when the sponsor could respond to additional questions, Dr. Noller said that the sponsor could respond as questions came up during the following discussion of the nine FDA discussion questions. (Note: The Panel opened the floor for the Open Public Hearing between Questions 6 and 7.)

Safety and Effectiveness

1. **The primary effectiveness endpoint for the pivotal study is the Symptom Severity Scale derived from the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL). Success was defined as a 10-point improvement in the Symptom Severity Scale of the UFS-QOL instrument in at least 50% of ExAblate® patients at 6 months. Is the 10-point improvement at 6 months a clinically meaningful measure of success?**

Dr. Diamond stated that he felt the 10-point improvement was not clinically significant, and that the study might have benefited from patients with more severe symptoms, possibly with higher initial SSS scores. The sponsor responded that the patients were significantly symptomatic and had significant uterine volume. Other panel members also expressed concern about the choice of 10 points. Panel members also suggested that the original follow up time should have extended past six months.

2. **The Intent-to-Treat (ITT) success rate at 6 months was 70.9% as indicated in the table below. The ITT success rate at 12 months was 40.4%. The success rate dropped in part due to patient loss-to-follow-up between 6 and 12 months. By 12 months, approximately 20% of the ExAblate® subjects had undergone alternative treatment for their fibroids.**

Intent-to-Treat Success Rates	
6 months	**77/109 (70.9%; 95% CI: 61.2 – 79.0)**
12 months	**44/109 (40.4%; 95% CI: 31.1-50.2)**

Secondary endpoints included fibroid volume changes at 6 months (ITT). On average, treated fibroid volumes decreased by 16%. Do the patient-reported outcome data from the Quality of Life instrument at 6 and 12 months, when coupled with the clinical result of actual volume reduction of treated fibroids, support the effectiveness of the ExAblate® for the treatment of uterine fibroids?

Panel members discussed the need to measure total uterine volume and whether measured decreases in fibroid volume are indicative of efficacy; some members said that fibroid volume is not always a final measure for efficacy in this case, as symptomatic relief can occur without a change in fibroid volume. Dr. Brown noted that while the volume changes were not impressive, there were still persistent effects at 12 months. The sponsor noted that uterine volume was only measured at baseline, and that measure of the profusion area and the fibroid's consistency are increasingly becoming the standard.

3. **Has the Sponsor demonstrated that MR thermal mapping provides adequate intraoperative feedback during the treatment regimen sufficient to ensure safe and reliable dosing to the intended fibroid tissue?**

Panel members generally agreed that the MR mapping does provide relatively reliable dosing. They had concerns about the thermal effect of adjacent sonications. The sponsor said that sonications are commonly done at adjacent sites; if the tissue does not fall to a baseline temperature in 90 seconds they will move on to another side of the fibroid and return to the adjacent site later. There was also concern that tissue damage from cavitations caused by bowel gas, for example, had not been adequately addressed. The sponsor reviewed cavitation monitoring provided in the device.

4. **A number of adverse events specific to ultrasound treatment occurred during the clinical trial, including nerve injury/leg pain and skin injury. Do the results from the thermal modeling and our understanding of the underlying physics provide sufficient information to understand the etiology of the injuries that occurred in the study?**

The panel felt that the explanation of adverse events on the skin was adequate but less so for an explanation of nerve damage and injuries. Panel members expressed concern about adverse effects on the patients' nerves related to distance from the bone and the incidence angle of the beam; FDA had earlier reported that a limit of 4 centimeters distance between the treatment focus and bone surface together with maintaining an incidence angle of 30 degrees or more would rarely produce adverse thermal effects. There were

also question about hot spots created by acoustic "side lobes." Sponsor said that the transducer design should preclude side lobes.

5. **Adverse events and other potential risks related to the use of the device prompted the development of active mitigations as identified in the attached chart. Are these mitigations sufficient to ensure safe use of the device? Given the effectiveness achieved, do the benefits outweigh the risks for this device?**

The Panel had questions about why the endometrial distance requirement was dropped in the continued access study. The sponsor said that they had not seen any endometrial damage throughout the protocol. The panel also had questions for the sponsor about increase in treatment volume, possible problems encountered due to the focal volume being allowed within the inner edge of the fibroid capsule in the continuing access study, and patient movement.

6. **Total abdominal hysterectomy (TAH) was selected as the "control group" in this study in order to allow for some comparison of rates of recovery and serious adverse events between ExAblate® and what has been seen historically as the standard of care for uterine fibroids. However, this was not a randomized study, and the ExAblate® patients differ significantly from the TAH patients in BMI, incidence of diabetes mellitus, hypertension, anemia, and other chronic conditions. Are the results of this study sufficient to demonstrate clinically meaningful comparisons regarding the safety of the ExAblate® procedure compared to TAH?**

Panel members generally agreed that no meaningful clinical comparisons for safety could be demonstrated from the control group; although a reasonable degree of safety has been demonstrated. Panel members differed on the possible value of a sham group to demonstrate efficacy, but there was general agreement that the design of the study made it difficult to know the device's real effect, especially because 33% of patients had undergone additional procedures by the 12-month follow-up.

OPEN PUBLIC HEARING

James B. Spies, M.D., professor of Radiology at Georgetown University and one of authors of the UFS-QOL spoke during the hearing, representing the Society of Interventional Radiology. Dr. Spies agreed with the panel that TAH does not necessarily provide appropriate comparison with the ExAblate® device, especially given that it is

rapidly loosing favor with many gynecologists, but he stressed the importance of using a questionnaire to evaluate fibroid symptoms. He noted that uterine and fibroid volumes do not always correlate with symptom change and that the outcomes from contrast-enhanced MRI provide a better predictor of procedure success. According to Dr. Spies, complete infarction of the fibroids is necessary for long-term success. He also urged the panel to consider including text on the device label that supports complete fibroid infarction.

Kleia R. Luckner, J.D., M.S.N., panel consumer representative, read into the record a statement from **Carla Dionne, executive director of the National Uterine Fibroid Foundation**. Ms. Dionne urged the Panel not to approve the device based on concerns about safety and efficacy, given that that the high loss-to-follow-up rate is well over the FDA's generally accepted rate of 15%; disappointing overall volume reduction and fibroid shrinkage; adverse events; questionable cost-benefit analysis for the treatment; and labeling concerns including exclusionary criteria. She suggested that the FDA continue to follow the pre-market use of the device for one year and develop a new study protocol comparative to other uterine-sparing procedures.

PANEL QUESTIONS (continued)

Labeling and Training

7. Does the panel have any comments on the labeling provided by the sponsor? Does the Panel have specific recommendations related to the proposed:

- **Indications**
- **Contraindications**
- **Warnings**
- **Precautions**
- **Adverse Events**
- **Clinical Study**

Panel members stated that the label should have the following: more detail on patient exclusion, including those with dense calcifications, intestines blocking the area, and large patients; indications such as location and number of fibroids; detailed information on possible nerve injury and damage; avoid using the term "standard of care"; detailed information on the treatment differences in the pivotal study versus the continued access study, especially that the focus of treatment needs to be 4 cm from the sacrum; alerting physicians to the fact that the nonprofuse volume was more than twice the region of treatment; information about the importance of light sedation and conscious feedback from patients; clearer and more detailed directions on what is required in training; and information in the patient brochure stating that the product is intended to treat the entire fibroid and additional information about benefits. The patient brochure should be rewritten in language that is simpler and more accessible; and the table outlining how this procedure compares with other procedures should be corrected.

8. FDA and the sponsor agreed upon procedural requirements during the pivotal trial and in the continued access study to mitigate safety-related concerns (see attached table). Is the ExAblate® training system sufficient to ensure that the proposed mitigations are followed?

Panel members stressed the need for extensive training and follow up for physicians, nurses, and other health care professionals involved in using the ExAblate® device.

Post-market Study

9. Under current FDA guidance, patients from the pivotal study are scheduled to be followed for a total of 3 years after the procedure (1 year pre-market and 2 years post-market), and up to 250 patients to be enrolled in the continued access study are scheduled to be followed for a total of 3 years after the procedure. Is there a need for additional post-approval studies or other post-market measures? If so, what is the purpose of such studies and what are the key elements of the study design?

Note: Post-approval studies may approve additional information about an approved device; however, the safety and effectiveness must be demonstrated before approval. The results of a post-approval study should not be expected to change the "approval" status of the device.

Panel members expressed interest in seeing post-market studies that would address the following areas: whether better results could be obtained by treating larger portions of the fibroids; a more diverse study population; increased objectified measures, such as menstrual blood loss; a recognition that this procedure will eventually be an adjunct to

enhanced fertility procedures requiring a registry; and the sponsor's data on uterine volumes in patients over time to see if there is a correlation between total uterine volume and patient success. However, Dr. Roberts urged caution in placing a burden on the sponsor by asking for additional enrollees in subsequent studies.

VOTE

Panel Executive Secretary Whang read the voting options. The panel voted 8-5 to recommend approval of the PMA with the following conditions:

1. The sponsor should provide analysis of data on uterine volumes and possible correlation with treatment failure. (Approved 11-0, 2 abstentions)
2. The sponsor and FDA should develop a strategy for assessing the impact of this procedure on future pregnancy; one suggestion was a registry. (Approved 10-0, 3 abstentions)
3. Physician labeling should prominently indicate how to minimize the risk of nerve injury. Patient labeling should explicitly indicate the possibility of nerve damage. (Approved 7-2, 4 abstentions)
4. Physician labeling should include additional description of training, including classroom time and phantom laboratory practice. (Approved 7-3, 3 abstentions)
5. Physician labeling should include additional information on the primary endpoint of the pivotal study and up-to-date references on the UFS-QOL. (Approved 10-0, 3 abstentions)
6. Physician labeling should include information on scars in the treatment area and the possible impact of previous Cesarean section. Data about the impact of previous

Cesarean section should be obtained from the clinical study. (Approved 9-1, 3 abstentions)

7. Physician labeling should indicate the importance of the level of patient sedation and the need to maintain continuous communication with the patient to reduce the risk of nerve injury. (Approved 13-0)

When explaining the rationale for their votes, some panel members stated that the short-term efficacy had been shown and the safety has been addressed adequately, especially given the restrictions and the mitigating efforts. Other panel members, however, were not convinced as to the device's effectiveness and the changes in quality of life measurements, especially given the short-term nature of the study, and expressed concern about possible placebo effect benefits. Other concerns were voiced, including the study's lack of a control group and the fact that there is no treatment algorithm for fibroids. Training to use this device must be strengthened and stressed, especially for nurses.

ADJOURNMENT

Dr. Noller thanked the participants for their hard work and adjourned the meeting at 4:30 p.m.

I certify that I attended this meeting of the Obstetrics and Gynecology Devices Advisory Panel Meeting on June 3, 2004, and that these minutes accurately reflect what transpired.

_____

Joyce M. Whang, Ph.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____

Kenneth L. Noller, M.D.
Chairperson

Summary prepared by
Susan C. Sanderson
5932 Lee Highway
Arlington, Virginia 22207
(703) 237-3696
astrobuddy@mindspring.com